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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/148,234	09/04/1998	IOANNIS MOUTSATSOS	P-4739-US	3002

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

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07/20/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/148,234	MOUTSATSOS ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/07/2010 has been entered.

Claims 1-23 and 29 have been cancelled.

Claims 24-28 are pending and under examination.

Claim Rejections - 35 USC § 112, 1st paragraph - enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 24-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The instant claims are drawn to a method of inducing organized, functional bone formation at a site of bone infirmity by implanting BMP-2-expressing (i.e., secreting) MSCs in the absence of a support osteoinductive matrix. However, neither the instant specification nor the art is enabling for the present claimed invention for the reasons discussed below.

In making the instant rejection, the following are noted:

An osteoinductive matrix is by definition a matrix comprising osteoinductive factors. No matrix is osteoinductive by itself; however, any matrix is rendered osteoinductive by the presence of osteoinductive factors (see Wolfe et al., Med. Prog. Technol., 1994, 20: 155-168, of record; p. 158, column 2, p. 159, column 1). In other words, it is the presence of osteoinductive factors that renders matrices osteoinductive. Thus, once in contact with MSCs genetically engineered to express and secrete BMP-2, non-osteoinductive matrices necessarily become osteoinductive and implanting such matrices is necessarily implanting MSCs in the presence of an osteoinductive matrix.

Therefore, by reciting implanting in the absence of an osteoinductive matrix, the claims practically recite implanting MSCs in the absence of any matrix (i.e., implanting MSCs alone). Inducing organized, functional bone formation at a site of bone infirmity by implanting MSCs without a matrix is not enabled by the art or the instant specification.

Bone formation cannot occur by simply implanting BMP-expressing MSCs in the absence of a support matrix (see Wolfe et al., p. 159). The art clearly teaches that organized, functional bone formation requires retaining the cells and the factors secreted by the cells for a sufficient time to promote repair and bone growth, which can be accomplish only by using a support matrix. For example, Bruder et al. (J Cell Biochem, 1994, 56: 283-294, of record) teach:

> "In order to effect osseous repair in a local defect, the cells must be delivered to the site in an appropriate carrier. We envision the ideal vehicle as biocompatible to minimize inflammation, osteoconductive to foster integration, resorbable to promote its own replacement, supportive of mesenchymal stem cell attachment and porous to facilitate rapid vascularization. In many ways, this vehicle would functionally resemble hypertrophic cartilage of the growth plate or fracture callus".

Along the same lines, Leach et al. (Expert Opin Biol Theor, 2004, 4: 1015-1027, of record) teach:

> "Transplantation of bone-forming cells to a repair site can promote bone regeneration by direct participation of these cells in bone formation and by the release of osteoinductive factors by these cells.
>
> The infusion or injection of transplanted cells is limited due to their potential to migrate away from the repair site, apoptosis or necrosis. Physical association with carriers in various forms has proven to be an effective means for maintaining bioactive factors and cells at the desired location for prolonged time."

Therefore, the art teaches that organized, functional bone formation cannot take place by simply implanting cells without a matrix.

Additionally, the instant specification fails to provide sufficient guidance for a skillet artisan on how to perform the claimed method. The specification provides only two examples of transplanting BMP-2-expressing cells without indicating whether a support matrix is used or not. Example 1 is directed to implantation into the abdominal muscle and not to a site of bone infirmity and therefore provides no guidance of how to induce functional bone formation at a site of bone infirmity by implanting cells in the absence of a support matrix. Example 2 is related to transplantation of cells into a 3 mm bone gap. However, Example 2 only discloses that BMP-2-expressing cells are localized at the gap site one week after transplantation; there is no evidence that functional bone formation occurred. The remaining Examples all teach the use of collagen sponges comprising BMP-2 (i.e., osteoinductive matrices). Therefore, the specification does not teach how to induce organized, functional bone formation by implanting the cells without an osteoinductive matrix at a site of bone infirmity. The art does not teach such. In fact the art teaches that functional bone formation requires osteoinductive matrices to bridge gaps larger than 1 mm (see Vaccaro et al., Spine J., 2002, 2: 206-215, p. 207, column 1 and paragraph bridging columns 1 and 2). It is noted that even Applicant's own work (i.e., Moutsatsos et al., Molecular Therapy, 2001, 3: 449-461, of record) provides evidence that only co-implantation with an osteoinductive matrix leads to the induction of functional bone formation (p. 455, column 1; p. 458, columns 1 and 2; p. 459, column 2; p. 460, column 1). Interestingly, Moutsatsos et al. described the same experiment as the one disclosed in Example 2 and demonstrate that only the use of an exogenously added osteoinductive matrix leads

to the healing of 3 mm gaps. Based on these teachings in the art and the lack of demonstration of functional bone formation in Example 2, one of skill in the art would not recognize that a gap of 3 mm could be healed by implanting BMP-2-expressing cells without a matrix. One of skill in the art would not recognize that implanting BMP-2-expressing MSCs in the absence of a support would lead to organized, functional bone formation as claimed. In conclusion, it is considered that the invention, as presently claimed is not enabled.

The applicant argues that examples 1 and 2 in the specification clearly show successful bone differentiation following transplantation of pluripotent stem cells transfected with BMP-2 in the absence of an exogenous osteoinductive matrix. In particular, Example 1 teaches that transplantation of pluripotent cells transformed with BMP-2 into the abdominal muscle leads to in vivo formation of bone collar and cartilage, prominent trabecular bone, cartilage and bone marrow, without the addition of an osteoinductive matrix. Further, Example 2 in the specification teaches that transplantation of pluripotent cells transfected with rhBMP-2 into a segmental defect results in the formation of ectopic bone in the absence of an exogenous osteoinductive matrix.

The lack of requirement for an osteoinductive matrix demonstrates that the transfected cells of the present invention possess an intrinsic ability to generate new bone tissue, a new and unexpected property. Accordingly, the specification provides

full enablement for bone formation following implantation of transfected cells without a matrix.

Furthermore, Moutsatsos discloses the following:

> Expression of rhBMP-2 in C3H10T1/2 cells can induce differentiation of osteoblastic and chondroblastic cells. These genetically engineered mesenchymal stem cells have an enhanced therapeutic effect in healing bone segmental defect due to a dual mechanism: the paracrine mechanism of rhBMP-2 on host cells and the autocrine mechanism of rhBMP-2 inducing the osteogenic differentiation of the transplanted genetically engineered stem cells themselves.
> Id. Paragraph bridging pages 449-50.

In addition, Moutsatsos teaches:

> Formation of bone by transplanted C9 cells expressing rhBMP-2 was achieved regardless of the carrier being used. C9 cells formed bone when transplanted on a biodegradable collagen carrier and even with no carrier at all when injected locally.
> Id, at page 460, col. 1.

Accordingly, Applicants' own work clearly demonstrates the ability of mesenchymal stem cells transfected with BMP-2 to induce bone formation in the absence of any matrix.

Moreover, as previously stated, Examples 3, 8, 9, 11 and 14-15 clearly show that implantation of collagen sponge alone or collagen sponge loaded with cells not expressing BMP-2 causes no bone formation. Contrary to the Examiner's allegation, nowhere do these examples show that the collagen sponge carrier used in the invention becomes osteoinductive.

The applicant argues that the Office's logic is flawed because the claims encompass the practice of a number of steps, not what occurs in the body after the final step is performed. Specifically, the claims recite the step of "implanting said cultured mesenchymal stem cell in the absence of an exogenously supplied osteoinductive

matrix at a site of bone infirmity." Therefore, at the time the cells are implanted, the matrix that the Office contends will hypothetically become osteoinductive is still not osteoinductive. Accordingly, the claims cover the use of non-osteoinductive matrices along with no matrix at all.

The applicant argues that Office failed to provide support for the allegation that non-osteoconductive matrices become osteoconductive It is possible that the matrix remains inert while the cells are the sole osteoinductive factor. Either way, the fact that the expression of BMPs by the claimed cells may eventually render a non-osteoinductive matrix osteoinductive is immaterial to the pending claims. The claims recite a method that may include the implantation of a matrix along with the cells, so long as that matrix is not osteoinductive when it is implanted.

The applicant argues that the examiner's assertion that Wolfe states that "bone formation cannot occur by simply implanting BMP-expressing MSCs in the absence of a support matrix is incorrect. Wolfe does not even discuss the therapeutic delivery of cells, let alone BMP-expressing MSCs. Wolfe's discussion of BMP induction of bone growth is limited to the delivery of osteogenic proteins themselves. Therefore, Wolfe's statement regarding the necessity of using a carrier substance is not relevant to the instant claims, which recite cells. One of skill in the art would clearly understand that the solubility of a protein therapeutic (Wolfe's reason for the necessity of a carrier) would not apply to the delivery of BMP-expressing cells. In fact, the cells perform at least some of the purposes of Wolfe's proposed carrier. The MSC cells of the instant

invention release BMP-2 over time and protect BMP-2 from non-specific proteolysis, just as with Wolfe' s carrier.

With respect to the passage cited from Bruder, the applicant argues that BMP-expressing MSCs are not discussed in this passage. Furthermore, Bruder clearly states that the matrix need not be osteoinductive, but can instead be osteoconductive. Therefore, Bruder does not teach that an osteoinductive carrier must be used in order to obtain organized functional bone formation. And even assuming that Bruder did explicitly state that, in their hands, they needed a carrier, its teachings are clearly contradicted by the instant specification, which shows bone growth and MSC retention in the absence of any carrier at all.

Finally, the Office cites Leach, stating that there is a problem with transplanting bone-forming cells because of their potential to migrate away from the repair site. Applicants do not dispute that carriers are an effective means for retaining cells at a repair site. But the fact that carriers work well does not mean that the MSCs of the instant invention cannot induce bone repair in their absence.

The applicant argues that the specification must only provide a teaching allowing a reasonable expectation of success of practicing the claimed invention without undue experimentation. As stated above, this burden has been met. In particular, the showing that the cells are localized to a bone defect gap site one week after transplantation is clear evidence that the cells are being retained--a key requirement for the carriers recited in Bruder, Wolfe, and Leach.

Finally, the Office mischaracterizes applicants' own work by stating that Moutsatsos provides evidence that only co-implantation with an osteoinductive matrix leads to the induction of functional bone formation. As pointed out in the previous reply and above, Moutsatsos clearly states that "C9 cells formed bone when transplanted on a biodegradable collagen carrier and even with no carrier at all when injected locally." This is supported by the data provided in Figure 6(g), which shows that "transplanted C9 cells were found lining newly formed bone trabeculi in the defect sites displaying the morphology of osteoblasts and expressing both β-gal and BMP-2..."

Taken singly or together, the references cited by the Office simply state that carriers are a good way to deliver osteogenic proteins or cells. But not a single one of these references shows any evidence that the methods of the invention won't work as claimed. They do not show the failure of any claimed methods, nor do they provide any reason why a person of ordinary skill in the art could not achieve organized functional bone formation by following the steps laid out in the claims. At best, they suggest that the use of a carrier may be more effective than no carrier, and at worst, they are entirely not relevant.

The applicant's arguments are acknowledged; however, they are not found persuasive for the following reasons:

The arguments regarding the Examples are not new and were previously addresses (see also the rejection above).

The applicant argues that Moutsatos demonstrates the ability of BMP-2-Transfected MSCs to induce bone formation in the absence of any matrix. This is not found persuasive. Moutsatos teaches induction of organized, functional bone formation at a site of bone infirmity only in the presence of a collagen carrier; there is no data indicating that organized and functional bone can be formed in the absence of the collagen carrier. The only time implantation occurs without a carrier is when the cells are implanted at sites other than bone defects, i.e., under the skin or in the abdominal muscle which results in ossicle formation (the cited paragraph, at page 460, col. 1 relates to these examples). However, the instant claims are drawn to the induction of organized, functional bone formation at a site of bone infirmity in a human and not to ossicles formation at any other site, which ossicles are not organized, functional bone. Therefore, Moutsatos's teachings do not enable the instant claims.

The applicant argues that, at the time the cells are implanted, the matrix is not osteoinductive. This is not found persuasive. Before implantation, the matrix is seeded with cells which secrete BMP, which secreted BMP is retained by the matrix. Therefore, at the time the matrix is implanted, the matrix is osteoinductive.

The applicant argues that Office failed to provide support for the allegation that non-osteoinductive matrices become osteoinductive This is not found persuasive. That non-osteoinductive matrices become osteoinductive when the necessary secreted factors are present is a well-known fact in the art and not an allegation.

The applicant argues that Wolfe's statement regarding the necessity of using a carrier is not relevant to the instant claims, which recite cells. This is not found

persuasive because the BMPs are secreted from the cells (i.e., cells cannot protect BMP from proteolysis); thus administering BMP-expressing cells in a carrier is equivalent to administering BMP in the carrier. Obviously, cells cannot replace a carrier because organized and functional bone formation at a site of bone infirmity cannot take place in the absence of a carrier (see the rejection above).

The applicant argues that, in the passage cited by the examiner, Bruder does not teach BMP-expressing MSCs or that an osteoinductive carrier must be used in order to obtain organized functional bone formation. This is not found persuasive. The fact that the passage does not specifically recite BMP-expressing MSCs or an osteoinductive carrier is immaterial. Bruder teaches that MSCs for bone repair must be delivered within a carrier (see p. 291, column 1, which includes the cited paragraph). Clearly, such teachings are material to the instant invention. Specifically, Bruder supports the assertion that organized and functional bone formation at a site of bone infirmity cannot occur in the absence of a carrier.

Please note that Leach et al. teach that bone formation in larger animals and humans can only be accomplished by using a support matrix (see the full p. 1016).

The applicant argues that none of the cited references shows any evidence that the methods of the invention won't work as claimed. In response, it is noted that the art as a whole indicates that bone regeneration at a site of bone infirmity cannot occur in the absence of a carrier and the instant specification does not provide any evidence to the contrary. Based on the teachings in the art and the lack of guidance in the

specification, one of skill in the art would not recognize that the claimed invention would work as claimed.

Conclusion

4. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633